PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
A-156736		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 03/02446	04.06.2003	10.06.2002

International Patent Classification (IPC) or both national classification and IPC

A61K9/00

Applicant

LABORATORIOS VITA, S. A.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.12.2003	23.09.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/02446

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 5-10, 12-24	as originally filed
3, 4, 11	received on 29.04.2004 with letter of 26.04.2004

Claims, Numbers

12 (part), 13, 14	as originally filed
1-11, 12 (part)	received on 29.04.2004 with letter of 26.04.2004

Drawings, Sheets

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

Section V

Reference is made to the following documents:
D1 - WO0112161, disclosing fast disintegrating tablets
D2 - NILSSON P ET AL: "PHYSICOCHEMICAL ASPECTS OF DRUG RELEASE V. THE IMPORTANCE OF SURFACE COVERAGE AND COMPACTION ON DRUG DISSOLUTION FROM ORDERED MIXTURES" INTERNATIONAL JOURNAL OF PHARMACEUTICS (AMSTERDAM), vol. 45, no. 1-2, 1988, pages 111-122
disclosing drug release in quick disintegrating tablets as a function of the choice of eccipients, surface and compaction;
D3 -MATTSSON S ET AL: "Formulation of high tensile strength rapidly disintegrating tablets: Evaluation of the effect of some binder properties" S.T.P. PHARMA SCIENCES 2001 FRANCE, vol. 11, no. 3, 2001, pages 211-220, disclosing ternary mictures with compound, microcrystalline cellulose and superdisintegrant
D4 - US5904937, disclosing taste masked oral admin forms with microcrystalline cellulose,
D5 - US5686107, disclosing tablets with improved texture and taste

Although some of the cited prior art documents disclose oral preparations with the same ingredients, none of them shows the same ratios . Insofar the subject-matter of present claims 1-14 can be considered novel as required by the PCT Art. 33(1) and (2).

D1, which is the closest prior art, discloses the same combination of ingredients in claim 14 (at least from a qualitative point of view) as in present claim 1; the difference is that claim 14 is silent about the amounts of said ingredients. It is also silent on the point whether mannitol is spray-dried or prepared according to another technique.
Therefore, it would not be considered obvious for the skilled person to choose spray-dried mannitol or the ratios of claim 1; the presence of an inventive step can be acknowledged under Art, 33(1) and (3) PCT.

29-04-2004

10/517110
IB0302446
JT12 Rec'd PCT/PTO 07 DEC 2004

<1>=<for oral administration>

or several hygroscopic agents and a direct compression soluble diluent. Said technology is registered as Flashtab® by Prographarm and is described in the patent EP 0548356.

d) Obtaining orally disintegrating tablets that disintegrate in the oral cavity in less than 60 seconds, and which contain spray-dried mannitol, crospovidone and other excipients, by direct compression. Said technology is described in the patent application WO 00/57857 by Yuhan Corporation.

However, all the above processes for obtaining tablets involve, to a greater or lesser extent, the following disadvantages:

- A high content of insoluble excipients or microencapsulated active ingredients that give the formula a gritty feel after they have been disintegrated in the oral cavity and, consequently, problems with palatability.
- Excessively long disintegration times in comparison with oral lyophilisates or wafers, which, in general, dissolve in less than 10 seconds.
- Insufficient mechanical resistance to resist conventional packaging and transport operations.

Description of the invention

A first aspect of the present invention is to provide ~~orally administered~~ tablets <1> that disintegrate quickly in the oral cavity, in particular, in less than 30 seconds, and which can hardly be noticed on the tongue after their disintegration.

A second aspect of the present invention is to provide a

process for obtaining said orally disintegrating tablets via direct compression, where direct compression is understood as a manufacturing process that involves sieving, mixing and compression operations only.

Detailed description of the invention

Surprisingly, the present invention has revealed that by using a diluent of high dissolution rate and high compressibility, and limiting the proportion and size of the particle of the insoluble ingredients, mixtures with optimum compressibility can be obtained. These mixtures enable the obtaining of orally disintegrating tablets which disintegrate in the mouth in less than 30 seconds, preferably less than 20 seconds, once they come into contact with saliva in the oral cavity, and which are hardly noticed on the tongue.

A further advantage is that the tablets described in the invention have sufficient mechanical resistance to resist the production and distribution operations, unlike other fast disintegration formulas such as oral lyophilisates, tablets of saccharide based shearform floss and wafers. The tablets of the invention have a friability of below 0.5%, preferably below 0.2%, as specified by Ph. Eur. 2.9.7. These friability values enable packaging in any kind of package using conventional machinery, and do not require any special care to be taken in the intermediate bulk storage of the tablets or in the feed systems used in the packaging operation.

As a result, the first aspect of the present invention relates to an ~~orally administered~~ tablet, as defined in the attached claims 1 to 11. <1>

A priori, there are no limitations to the active ingredients in this invention, although the active

- A disintegration time in the oral cavity of below 30 seconds, preferably below 20 seconds.
- An apparent density from 1.1 to 1.3 g/ml.

The apparent density of the tablets is calculated by means of the division of the mass (m) by the volume (.e.g. $V=\pi \cdot r^2 \cdot h$, if the tablet is flat and round like the preferable shape proposed in this invention, where r is the radius and h the thickness of the tablet). It has been shown that the apparent densities of the tablets obtained with the compositions of the present invention correlate to the resistance to breakage of the tablets and to their disintegration time in the mouth. It has also been shown that tablets with apparent densities from 1.1 to 1.3 g/ml make it possible to guarantee the specifications of friability and disintegration, which is the aim of the present invention.

It has also been observed that in order to guarantee fulfilment of the specification of the disintegration time in the oral cavity, the tablets should disintegrate in less than 40 seconds in the *in vitro* disintegration test described in the tablet characterisation section of the Experimental Section of the present invention.

As mentioned previously, the present invention also relates to a process for obtaining said orally disintegrating tablets comprising direct compression. The tablets described in the invention are obtained by compression of a powder blend into solid form, which dimensions and shape enable even further minimisation of disintegration time.

In particular, the process for obtaining an ~~orally administered~~ tablet, as previously defined comprises the

29-04-2004

10/517110 IB0302446

JT12 Rec'd PCT/PTO 07 DEC 2004

<1> = < for oral administration >

CLAIMS

1. ~~Orally administered~~ Tablet <1> that disintegrates quickly in the oral cavity in less than 30 seconds, comprising:

i) Spray-dried mannitol in a proportion of at least 59.5%;

ii) active ingredient in a proportion below or equal to 10%, as a fine powder in which at least 90% in weight of the active ingredient has a particle size less than 100 µm;

iii) Microcrystalline cellulose in a proportion from 10 to 18%, with an average particle size of approximately 50 µm where at least 99% in weight of microcrystalline cellulose has a particle size below 250 µm;.

iv) Sodium croscarmellose in a proportion from 1 to 4%; and

v) A lubricant agent in a proportion from 0.5 to 2% in weight,

where, unless specified otherwise, the percentages are expressed in weight of the total weight of the tablet.

2. ~~Orally administered~~ Tablet <1> according to claim 1, characterised in that it has a friability below 0.5% according to Ph. Eur. 2.9.7.

3. ~~Orally administered~~ Tablet <1> according to claim 2, characterised in that it has a friability below 0.2% according to Ph. Eur. 2.9.7.

4. ~~Orally administered~~ Tablet <1> according to claim 1, characterised in that it has an apparent density from 1.1 to 1.3 g/ml.

5. ~~Orally administered~~ Tablet <1> according to claim 1, characterised in that it has a flavouring agent in a proportion from 0.5 to 2% in weight of the total weight of the tablet.

6. ~~Orally administered~~ Tablet <1> according to claim 5, characterised in that it has an artificial sweetener in a proportion from 0.5 to 2% in weight of the total weight of the tablet.

7. ~~Orally administered~~ Tablet <1> according to claim 1, characterised in that it has a humidity adsorbing agent in a proportion from 0.1 to 0.5% in weight of the total weight of the tablet.

8. ~~Orally administered~~ Tablet <1> according to claim 1, characterised in that it has an anti-adherent agent in a proportion from 0.5 to 2% in weight of the total weight of the tablet.

9. ~~Orally administered~~ Tablet <1> according to claim 1, characterised in that the proportion of insoluble elements is below 20% in weight of the total weight of the tablet.

10. ~~Orally administered~~ Tablet <1> according to any of previous claims, characterised in that it has a round shape, flat, bevelled with a thickness from 1,8 to 2.2 mm.

11. ~~Orally administered~~ Tablet <1> according to claim 10, characterised in that it disintegrates quickly in the oral cavity in less than 20 seconds.

12. Process for obtaining an ~~orally administered~~ tablet as defined in any of claims 1 to 11, characterised <1>